Advanced CoMFA®

REFINE AND ENHANCE 3D QSAR MODELS

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The basic tools needed to build powerful, predictive models of biological activity (or any other property) from molecular structure are provided in SYBYL®'s QSAR module. These include molecular field generation tools, least-squares (PLS, PCA, and SIMCA) and non-linear (hierarchical clustering) analysis tools. The most powerful of these techniques can be extended, and their application automated, using the Advanced CoMFA module. These expert analysis tools allow the capture of more chemical information pertinent to the successful prediction of activity. The expert graphics tools in Advanced CoMFA allow easier communication of results to other team members, and to the larger scientific community.

More Types of Molecular Fields

In addition to steric and electrostatic fields, Advanced CoMFA can calculate several new types of fields. Hydrogen bonding fields[1] are created by assigning energies equal to the steric cutoff energy to lattice points that are close to H-bond accepting or donating atoms. Indicator fields[2] are used to convert continuous data to discrete. Parabolic fields are created by squaring the original field at each lattice point, but retaining the sign of the original field.

Increased Accuracy and Clarity

Region Focusing is a new technique that allows you to increase the resolution (decrease the lattice spacing) of CoMFA models without sacrificing predictive ability. Basically, the lattice points in a CoMFA region are weighted to enhance or attenuate their contribution to subsequent analyses. By carefully selecting the weighting parameters and sharpness of focusing, PLS calculations become practical at much finer grid resolutions than ever before.

Region Focusing also removes clutter from visual representations, and greatly enhances the clarity of presentations by emphasizing the relevant field regions.

Optimized Leads and Libraries

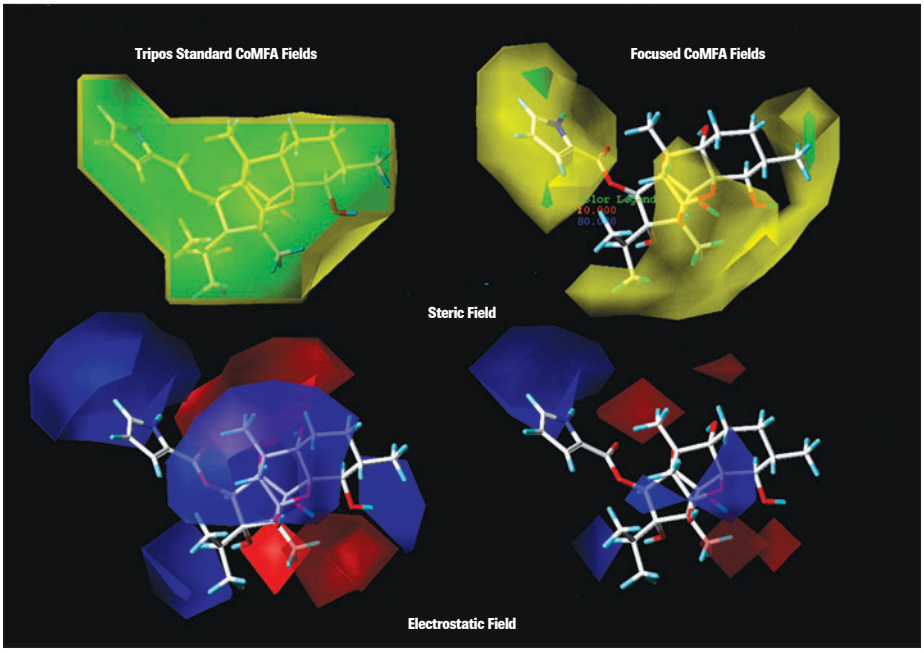
Lead compounds can be optimized against a CoMFA model by systematically searching for optimal substitution patterns. Combinatorial libraries can be optimized against an established CoMFA model, using a random walk, additive, exhaustive, or file-driven search pattern.

Better Management of Clustering Analyses

Hierarchical analysis has been extended in Advanced CoMFA to include better tools for manipulating clusters. In particular, a dendogram can be "cut" at any level of resolution to produce an MSS column. A provision is made for dispersing, or "fuzzifying," these cluster indices to facilitate picking points graphically. Clusters can be nested across several levels of resolution to provide a partial ordering. The cluster columns in SYBYL's Selector™ module can also be used for automated selection. Advanced CoMFA supports direct access to cluster memberships, as well as direct output to the Molecular Spreadsheet.™

Advantages

- More field classes and cluster management tools
- Techniques for improving weak models
- Region Focusing to increase model resolution and visual clarity
- Enhanced tracking of analysis results
- Ability to survey combinatorial libraries for prospective leads



Advanced CoMFA allows focusing of standard steric and electrostatic CoMFA fields on spatial regions which best describe variation in biological activity.

Track Analyses

Advanced CoMFA creates an analysis table, and automatically adds each new analysis. All results and parameters are included, making it easy to compare the results of different analyses. PLS, PCA, SIMCA, and hierarchical clustering analyses can be included.

Hardware and Software Requirements

Advanced CoMFA requires a separate license in addition to a license for SYBYL/Base. Advanced CoMFA and SYBYL/Base run on workstations operating under IRIX® (SGI®) or Linux® (x86).

Complementary Software

- **Almond™** for calculating and utilizing alignment independent molecular descriptors.
- **AMPAC™** for calculating transitional states and spectral properties using semiempirical quantum mechanical methods.
- **ClogP/CMR** for including molar refractivity and logP in QSAR and ADME models.
- **Confort™** for generating sets of diverse, low energy conformers.
- **Distill™** for determining and visualizing SARs.
- **hint!®** for analyzing hydropathy and hydropathic interactions.
- **HQSAR™** for performing automated QSAR analyses.
- **LeapFrog®** for performing *de novo* ligand design.
- **MM3™/MM4™** for optimizing structures by molecular mechanics.
- **Molconn-Z™** for computing a wide range of topological indices based on molecular structure.
- **QSAR with CoMFA** for building predictive structure-activity and structure-property models.
- **Selector** for characterizing and sampling compound libraries.
- **VolSurf™** for predicting ADME properties.
- **ZAP™** for calculating and displaying the electrostatic potential of molecules.

References

1. Bohacek, R. S.; McMartin, C. "Definition and Display of Steric, Hydrophobic, and Hydrogen-Bonding Properties of Ligand Binding Sites in Proteins Using Lee and Richards Accessible Surfaces: Validation of a High-Resolution Tool for Drug Design." *J. Med. Chem.* **1992**, *35*, 1671-1684.
2. Kroemer, R.T.; Hecht, P. "Replacement of steric 6-12 potential-derived interaction energies by atom-based indicator variables in CoMFA leads to models of higher consistency." *J. Comput.-Aided Mol. Design* **1995**, *9*, 205-212.

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